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ORIGINAL PAPER

# Insulin sensitivity and first-phase insulin secretion in obese Chinese with hyperglycemia in 30 and/or 60 min during glucose tolerance tests

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**Abstract** The purpose of this study was to investigate insulin sensitivity and first-phase insulin secretion in obesity with hyperglycemia in 30 and/or 60 min during oral glucose tolerance (OGTT, glucose $\geq$ 11.1 mmol/l, post-loading hyperglycemia, PLH) in Chinese population. A total of 196 nondiabetic subjects were included in the present study, among them 99 had normal glucose tolerance (NGT, subdivided into 32 lean NGT and 67 obese NGT), 74 had obesity with impaired glucose tolerance (IGT) and 23 had obesity with PLH. A standard 75-g oral glucose tolerance test was performed after fasting and at 30 min, 1, 2 and 3 h. Insulin sensitivity index ($S_I$) was assessed by the Bergman's minimal model method with frequently sampled intravenous glucose tolerance test (FSIGTT), insulin secretion was determined by acute insulin response to glucose (AIRg). The disposition index (DI), the product of AIRg and $S_I$ was used to determine whether AIRg was adequate to compensate for insulin resistance. $S_I$ was significantly equally lower in three obese subgroups. AIRg was significantly increased in obese NGT as compared with lean NGT controls, and reduced to the same extent in IGT and PLH subjects. There was no significant difference among lean NGT, IGT and PLH subjects. DI value was reduced from obese NGT individuals, IGT and PLH subjects had a similar lower level of DI. In conclusion, our present results demonstrated that the pathophysiological basis of obese subjects with PLH were clearly insulin resistance and defective in first-phase insulin secretion as that in IGT subjects in Chinese population.

**Keywords** Obesity · Impaired glucose tolerance · Post-loading hyperglycemia · Insulin resistance · Acute insulin response to glucose

## Introduction

Type 2 diabetes mellitus (T2DM) is a heterogeneous disorders characterized by a dual pathogenetic mechanism: insulin resistance and defects in $\beta$-cell function [1]. The course of T2DM is slow and the metabolic abnormalities, which lead to hyperglycemia per se are established long before clinical diabetes develops. This state, where abnormalities in glucose homeostasis are present but elevation in plasma glucose concentration, is below the cutoff point of establishing the diagnosis of T2DM is referred to as pre-diabetes [2]. Pre-diabetes includes individuals with impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and combination of both IGT and IFG [3]. Nowadays, it is well accepted that the pathophysiological abnormalities of these pre-diabetes also includes both reduced insulin sensitivity and impaired $\beta$-cell function [4–6]. Subjects with IFG predominantly manifest liver insulin resistant while subjects with IGT predominantly manifest muscle insulin resistant [7]. In epidemiological studies, subjects with isolated IGT and isolated IFG had similar risk for progression to T2DM [8]. Our previous study has shown that cardiovascular disease may be more strongly related to post-challenge hyperglycemia rather than fasting hyperglycemia [9].

Jie Hong and Yi-fei Zhang contributed equally to this work.

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Currently, the diagnosis of glucose metabolic abnormalities is mainly based on the fasting and 2-h plasma glucose concentrations from a 75-g oral glucose tolerance test (OGTT) according to the World Health Organization/American Diabetes Association criteria [3], and OGTT is the most commonly used method to evaluate whole body glucose tolerance to identify people with undiagnosed asymptomatic diabetes, meanwhile to assess insulin secretion and insulin sensitivity in vivo. However, the information provided at different time points other than at 2-h during OGTT seems to have attracted little attention. In clinical practice, we can often find those subjects with normal fasting and 2-h glucose concentrations but elevated glucose level whether in 30 or 60 min during OGTT. Recently, Tian et al. found that the progression to T2DM and IGT for people with plasma glucose level greater than 11.1 mmol/l in OGTT was 9.9% and 40.6%, respectively, in a retrospective study in 192 Chinese subjects and the average duration for following up was 7 years (according to 2003 Chinese Medical Association Diabetes Association's ninth National Diabetes Academic Conference Papers Series). Based on this preliminary result, we hypothesized that subjects with hyperglycemia in 30 and/or 60 min during OGTT (glucose $\geq$ 11.1 mmol/l, post-loading hyperglycemia, PLH) may be a specific categories of glucose metabolic disturbance and we tested this hypothesis in our present study. The purpose of this study was to investigate insulin sensitivity and first-phase insulin secretion in obesity with PLH compared to subjects with normal glucose tolerance (NGT) and IGT in Chinese population by using the standard OGTT and a direct measure of insulin resistance and first-phase insulin secretion of $\beta$-cell with an insulin-modified frequently sampled intravenous glucose tolerance test (FSIGTT) in conjugation with Bergman's minimal model analysis, meanwhile to assess whether it is possible to identify more pre-diabetic subjects before they fall into the criteria of WHO and ADA.

## Results

### Clinical characteristics

The anthropometric and metabolic characteristics of the 196 subjects including lean NGT, obese NGT, obese IGT and obese PLH according to their glucose tolerance status are shown in Table 1. There was no statistically significant difference between groups with respect to mean age and gender, whereas BMI, systolic blood pressure and fasting serum triglycerides, total cholesterol concentrations were not significantly different among obese NGT, IGT and PLH subjects, in all of whom it was significantly greater than in lean NGT controls, and HDL concentrations were equally lower in those three obese groups as compared with lean NGT controls. IGT and PLH subjects had higher LDL concentrations and diastolic blood pressure than in lean NGT, and there was no statistically significance between both NGT groups, the diastolic blood pressure in PLH group was even higher than in IGT group. Though waist circumference was significantly greater in those three obese subgroups, and obese subjects with PLH had even higher waist circumference than obese NGT and IGT subjects.

### Plasma glucose and insulin concentrations

Plasma glucose and insulin concentrations during the OGTT are displayed in Fig. 1a and b, respectively. Blood glucose levels were significantly higher in IGT and PLH than in both two NGT groups in OGTT at fasting, 30 and 60 min. As expected, individuals with PLH had higher levels of 30 and 60 min and lower levels of 2-h glucose concentrations than IGT individuals. Two-hour glucose level was higher in obese NGT and PLH groups as compared with that in lean NGT group. Subjects with PLH had a lower 3-h glucose level than IGT subjects and obese NGT subjects. There was no significant difference between lean NGT and PLH group (Fig. 1a; Table 1).

Compared with lean NGT group, insulin levels were significantly equally higher in those all three obese subgroups in OGTT at 0, 30, 60, 120 and 180 min (Fig. 1b; Table 1).The plasma insulin response rose progressively from 30 to 60 min in both of the two NGT groups and PLH group, yet the plasma insulin response to glucose loading was delayed and rose progressively from 60 to 120 min in IGT group.

### Indexes of insulin resistance

Insulin resistance, calculated by HOMA-IR, was significantly higher in subjects with obese NGT, IGT and PLH compared with lean NGT individuals. However, there was no significant difference among those latter three obese groups (Table 1). As determined by the direct measurement of insulin sensitivity from FSIGTT in conjugation with Bergman's minimal model method, the $S_I$ value in lean control group was significantly higher than in obese NGT, IGT and PLH group, also there was no significant difference among those three obese subgroups (Table 1). It suggested that obese subjects with NGT, IGT and PLH all presented the same extent of insulin resistance.

### Beta cell function

The early-phase (0–30 min) insulinogenic index expressed as $I_{0-30}/\Delta G_{0-30}$ was increased significantly in obese NGT and PLH group than in lean NGT controls (Table 1), and obese subjects with NGT had an even higher $\Delta I_{0-30}/\Delta G_{0-30}$ than

**Table 1** Characteristics of the subjects according to the 75-g OGTT and the FSIGTT

| Clinical and metabolic data | LN/NGT | OB/NGT | OB/IGT | OB/PLH |
|---|---|---|---|---|
| Number | 32 | 67 | 74 | 23 |
| Gender (M/F) | 15/17 | 30/37 | 34/40 | 12/11 |
| Age (years) | 36.1 ± 10.3 | 32.0 ± 12.5 | 36.1 ± 12.4 | 36.5 ± 13.7 |
| Body mass index (Kg/m$^2$) | 20.6 ± 1.4 | 31.4 ± 4.3* | 30.1 ± 3.6* | 33.4 ± 5.4* |
| Waist circumference (cm) | 72.9 ± 5.4 | 95.1 ± 11.3* | 92.6 ± 8.8* | 104.7 ± 12.6*$^{\#\S}$ |
| Systolic blood pressure (mmHg) | 110.7 ± 12.6 | 121.8 ± 16.2* | 121.9 ± 15.9* | 133.3 ± 18.0* |
| Diastolic blood pressure (mmHg) | 72.4 ± 8.0 | 77.9 ± 10.8 | 80.6 ± 10.7* | 89.3 ± 12.4*$^{\#\S}$ |
| Oral glucose tolerance test (OGTT) | | | | |
| Fasting glucose (mmol/l) | 4.73 ± 0.53 | 4.99 ± 0.47 | 5.30 ± 0.52*$^{\#}$ | 5.33 ± 0.42*$^{\#}$ |
| 30-min glucose (mmol/l) | 7.89 ± 1.15 | 8.40 ± 0.96 | 9.50 ± 1.57*$^{\#}$ | 10.9 ± 1.36*$^{\#\S}$ |
| 60-min glucose (mmol/l) | 6.82 ± 1.54 | 7.70 ± 1.35* | 10.89 ± 1.63*$^{\#}$ | 11.87 ± 1.32*$^{\#\S}$ |
| 2-h glucose (mmol/l) | 5.09 ± 0.86 | 6.00 ± 0.97* | 9.04 ± 0.89*$^{\#}$ | 6.15 ± 1.21*$^{\S}$ |
| 3-h glucose (mmol/l) | 3.95 ± 0.73 | 4.29 ± 0.96 | 5.31 ± 1.53*$^{\#}$ | 3.74 ± 0.58$^{\#\S}$ |
| Fasting insulin (μU/ml) | 7.3 ± 5.0 | 17.4 ± 13.2* | 15.8 ± 10.6* | 18.8 ± 13.9* |
| 30-min insulin (μU/ml) | 46.9 ± 34.1 | 175.9 ± 101.4* | 93.5 ± 68.3*$^{\#}$ | 137.0 ± 73.1* |
| 60-min insulin (μU/ml) | 45.9 ± 19.4 | 178.2 ± 94.2* | 147.2 ± 111.0* | 252.6 ± 183.5* |
| 2-h insulin (μU/ml) | 24.7 ± 10.3 | 116.0 ± 92.0* | 167.8 ± 139.7* | 135.7 ± 123.7* |
| 3-h insulin (μU/ml) | 11.2 ± 7.0 | 37.9 ± 37.3* | 83.1 ± 168.9* | 32.5 ± 31.5* |
| HOMA-IR (μUmol/l$^{-2}$) | 1.60 ± 1.20 | 4.37 ± 5.07* | 3.84 ± 2.62* | 4.53 ± 3.21* |
| $\Delta I_{0-30}/\Delta G_{0-30}$ (μU/ml per mmol/l) | 13.3 ± 12.2 | 49.3 ± 29.2* | 19.7 ± 17.7$^{\#}$ | 23.5 ± 12.3*$^{\#}$ |
| $S_I \times 10$ (min$^{-1}$ mU$^{-1}$l) | 7.67 ± 2.97 | 1.81 ± 1.11* | 1.64 ± 1.08* | 1.54 ± 1.34* |
| AIRg (mU l$^{-1}$ min) | 431.6 ± 175.5 | 1223.4 ± 802.9* | 506.8 ± 363.1$^{\#}$ | 684.5 ± 571.4$^{\#}$ |
| Disposition index | 2967.3 ± 1050.0 | 1868.4 ± 1119.1* | 700.7 ± 567.6*$^{\#}$ | 777.7 ± 643.6*$^{\#}$ |
| Triglycerides (mmol/l) | 0.89 ± 0.29 | 1.79 ± 0.92* | 1.97 ± 1.53* | 2.28 ± 1.15* |
| Total cholesterol (mmol/l) | 3.98 ± 0.91 | 4.68 ± 0.95* | 5.02 ± 0.74* | 5.16 ± 1.09* |
| HDL cholesterol (mmol/l) | 1.59 ± 0.24 | 1.25 ± 0.27* | 1.26 ± 0. 26* | 1.25 ± 0.29* |
| LDL cholesterol (mmol/l) | 2.31 ± 0.53 | 2.76 ± 0.83 | 3.01 ± 0.75* | 3.15 ± 1.04* |

Data are means ± SD. * $P$ <0.05 versus LN/NGT group, $^{\#}$ $P$ <0.05 versus OB/NGT group, $^{\S}$ $P$ <0.05 versus OB/IGT group

PLH and IGT subjects. There was no significant difference between lean NGT and IGT, IGT and PLH subjects (Table 1). The similar results were further observed by the first-phase insulin secretion as determined by AIRg. It was significantly higher in obese NGT individuals than in other three groups (Table 1), and the latter three groups had a similar value of AIRg, although obese subjects with IGT and PLH secreted nearly as much insulin as lean NGT controls in response to the bolus to glucose (AIRg), this response was obviously insufficient for their degree of insulin resistance, as indicated by the markedly lower DI (Table 1), and the DI value almost equally decreased in these two groups. However, the value of DI in obese NGT subjects was significantly lower than in lean NGT controls and higher than in IGT and PLH subjects.

## Discussion

The OGTT is a widely used procedure that was originally developed to classify carbohydrate tolerance and is also used to evaluate insulin release and insulin resistance in various clinical settings. The 1997 ADA and 1999 WHO criteria lowered the fasting plasma glucose level for the diagnosis of diabetes from ≥7.8 to ≥7.0 mmol/l to facilitate identification of undiagnosed diabetes and to reduce the discrepancy between fasting glucose and 2-h glucose cutoff points used in an OGTT [10]. Using of fasting glucose was advocated by the ADA because it is a much simpler test than an OGTT and can be widely applied in clinical practice and because of its predictive value for microvascular complications is nearly the same as that of 2-h glucose [10]. The WHO in 1999, however, advocated retention of the OGTT for the diagnosis of diabetes and staging of impaired glucose regulation.

In China, we also adopt 75-g OGTT to screen for diabetes, and often measure blood glucose level at 0, 30, 60, 120 and 180 min. Up to now, no sufficient data available to insight the role of PLH in 30 and/or 60 min during OGTT in the transition from NGT to overt diabetes mellitus. Our present results demonstrated that the pathophysiological

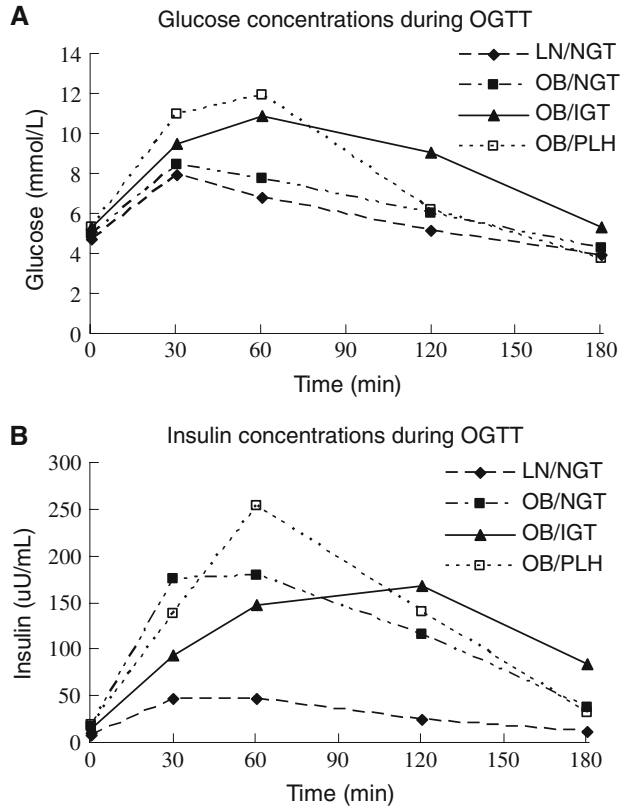


**Fig.1** **a** Glucose concentrations during OGTT, **b** insulin concentrations during OGTT

basis of obese subjects with PLH were clearly insulin resistance and defective in first-phase insulin secretion as that in IGT and diabetes.

The euglycemic–hyperinsulinemic clamp studies are the generally accepted method which can directly measure insulin sensitivity and $\beta$-cell function, but these are complicated procedures, and they are generally impractical for use outside of specialized research centers [11]. Bergman's minimal model of glucose kinetics, in conjunction with insulin-modified FSIGT, is widely used to detect insulin sensitivity and $\beta$-cell secretory capacity in subjects with IGT and type 2 diabetes mellitus in both clinical and epidemiological studies. By using reduced sampled number ($n = 12$) of Bergman's minimal model method in combination with insulin modified FSIGTT, our data have shown that insulin sensitivity index ($S_I$) was significantly decreased in the same extent in obese subjects with NGT, IGT, and PLH compared with lean NGT controls. Among epidemiological studies, insulin sensitivity usually has been evaluated with surrogate measures, most commonly HOMA-IR. HOMA-IR values are derived in the basal state and can therefore be considered to reflect basal or hepatic insulin sensitivity [12]. In the present study, we find that obese subjects with NGT, IGT and PLH had an equally significant elevation of HOMA-IR compared with lean NGT controls. These results have suggested that obese subjects with PLH have a similar degree of insulin resistance to obese subject with IGT.

In our present study, we find that although the peak insulin response after oral glucose loading was at 30–60 min in both of the two NGT groups and PLH group, yet the magnitude of the response was different, obese subjects with NGT and PLH had a higher insulin response than lean NGT subjects. For subjects with IGT, the peak value was at 60–120 min, as a result, the plasma glucose concentration continued to increase after 60 min and remained elevated at the 120 min. In contrast, the incremental rise in plasma glucose concentration was at 30–60 min in subjects with PLH, and at 120 min the plasma glucose concentration returns to a value similar to obese NGT. The $\Delta I_{0-30}/\Delta G_{0-30}$, was significantly increased in obese NGT group, though this index was significantly higher in PLH than in lean controls, and there was no significant difference between IGT and PLH, IGT and lean NGT groups.

The loss of early phase insulin secretion may be a key factor in postprandial hyperglycemia as well [13]. In our current study, we find that AIRg, reflecting first-phase insulin secretion, was significantly lower in both obese IGT and PLH subjects as compared with obese NGT subjects (see in Table 1). Although these obese subjects with IGT and PLH secreted nearly as much insulin as the lean NGT controls in FSIGTT, this response was clearly inadequate for their degree of insulin resistance, as presented by the markedly lower disposition index (DI). The DI, usually calculated as the product of insulin sensitivity and insulin secretion, has been proposed as a measurement of the overall compensatory response of $\beta$-cell to insulin resistance. Lower levels represent an inability of the pancreas to secret enough insulin at that level of insulin resistance [14]. Our finding has thus suggests that obese subjects with IGT and PLH have a similar degree of deficiency in first-phase insulin secretion.

In the present study, we examined the insulin action and secretion in obese subjects with PLH in 30 and/or 60 min during OGTT (PLH) by direct measure of insulin resistance and first-phase insulin secretion of $\beta$-cell with FSIGTT. And similar report has not been found up to now. We have shown that Chinese obese subjects with isolated IGT and isolated PLH have a similar degree of insulin resistance and deficiency of insulin secretion. As compared with lean healthy controls, obese subjects with PLH and IGT had abnormalities in lipid profiles and blood pressure levels, respectively. Long-term studies are needed to follow up this group of subjects. In terms of limitations, we could not further subdivide the subjects into isolated 30 and 60 min hyperglycemia to elucidate the pathophysiological abnormalities underlying these two kinds of status due to the relatively small samples of subjects. On the other hand, the

pathophsiological basis of PLH may be different according to the different ethnic study populations, if the results of our study are confirmed in other populations, this knowledge could warrant clinical attention and influence preventive treatments targeted at high-risk individuals of type 2 diabetes mellitus.

## Materials and methods

### Subjects

For inclusion in the present study, we considered consecutive patients who were referred to the specialized outpatient clinic for overweight and obesity in Ruijin Hospital affiliated to Jiaotong University School of Medicine, Shanghai, China. In the period from June 2003 to December 2006, 264 obese nondiabetic patients and 38 lean healthy volunteers from our hospital were enrolled in the present study. Of these 302 study participants, 106 were excluded because FSIGTT was not performed ($n = 45$), or because they matched criteria of IFG only or IFG + IGT ($n = 61$). Thus, this study included 196 subjects (164 from our overweight and obesity outpatient clinic and 32 lean healthy normal volunteers).

We defined all subjects were as unrelated Chinese Han nationality living in Shanghai region and were excluded from the study if they had known diabetes or were taking any medication that affects glucose tolerance or for infections, liver or kidney disease, or thyroid function disorder. Body weight was stable (±2 kg) for at least 3 months before study in all subjects. This study was performed in accordance with the Helsinki declaration and was approved by the Institutional Review Board of Rui-Jin Hospital affiliated to Jiaotong University School of Medicine, Shanghai, China. Written informed consent was obtained from each participant.

### Methods

All subjects underwent a standard 75-g OGTT at their first visit after a 10-h overnight fast. Blood samples were obtained at 0, 30, 60, 120 and 180 min after the glucose load. Subjects were classified as NGT group (fasting glucose <6.1 mmol/l and 2-h glucose <7.8 mmol/l and glucose level below 11.1 whether in 30 or 60 min) who was further subdivided into lean healthy controls (LN, $n = 32$) and obese NGT ($n = 67$) according to their body mass index, IGT group ($n = 74$) was diagnosed when fasting glucose <6.1 mmol/l and 2-h glucose between 7.8 and 11.1 mmol/l according to the 1999 World Health Organization criteria. PLH group ($n = 23$) was defined as fasting glucose <6.1 mmol/l, 2-h glucose <7.8 mmol/l and glucose ≥ 11.1 mmol/l whether in 30 and/or 60 min. On the day of OGTT, body weight was measured to the nearest 0.1 kg using a platform digital scale. Subjects were weighed light clothed without shoes, measurements of the waist at the smallest abdominal circumference. Circumference measurements were performed twice and the mean value reported. Lipid profile was also collected after an overnight fast at the first visit. The diagnosis of obesity was based on the criteria of Asia-Oceania [15], which was defined by a BMI greater than or equal to 25 kg/m$^2$.

On the second visit day, subjects underwent an insulin-modified FSIGTT (OGTT and FSIGTT were performed 3 days apart). None of the participants consumed alcohol, cigarette and refrained from heavy physical exercise for at least 1 week before the test, and all subjects took diets containing at least 250 g carbohydrate for consecutive 3 days before the test.

### The frequently sampled intravenous glucose tolerance test

For the FSIGTT, as described previously [16–18], after a 10-h overnight fast, a flexible catheter was inserted into each antecubital vein between 7 and 8 o'clock in the following morning for blood sampling and for glucose and insulin administration, respectively. Subjects were allowed to rest calmly for at least 15 min before test initiation. Then 50% glucose (300 mg/kg) was administered intravenously (iv) within 2 min, and 18 min later, subjects received an iv bolus of regular human insulin 0.03 U/kg (Actrapid; Novo Nordisk) over 60 s. Blood samples were drawn frequently from the contralateral antecubital vein at 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 90 and 180 min after administration of glucose. Serum was frozen at −20°C for subsequent analysis. Glucose and insulin concentrations were then entered into the Bergman MINIMOD computer program to obtain quantitative estimates of the insulin sensitivity index.

### Laboratory analytic methods

Plasma glucose level was determined immediately after blood centrifugation with a Beckman CX-7 automatic biochemical analyzer by the glucose oxidase method with intra-assay CV <2.6%, inter-assay CV <4.2%. Serum insulin level was measured in duplicate using a radioimmunoassy with intra-assay CV <4.2%, inter-assay CV <7.6% (Sangon Company, Shanghai, China). Serum total cholesterol and triglycerides were measured by the enzymatic method, and high-density lipoprotein (HDL) cholesterol was measured using specific precipitation method (Beckman LX-20, Brea, CA, USA).

### Insulin resistance

Insulin resistance was determined by HOMA-IR from OGTT and by the insulin sensitivity index ($S_I$) calculated from the insulin-modified FSIGTT using the minimal model equations.

### Insulin secretion

The insulinogenic index, which was a widely used index of early-phase insulin response, was defined as the ratio of the increment of plasma insulin to that of plasma glucose at 30 min after glucose loading the OGTT ($\Delta I_{0-30}/\Delta G_{0-30}$). The acute insulin response to glucose (AIRg) during FSIGTT was calculated as the area under the insulin curve over basal concentration from 0 to 10 min. The DI, which is the product of AIRg and $S_I$ was used to determined whether AIRg was adequate to compensate for the degree of insulin resistance.

### Statistical analysis

Analyses were performed using the SPSS 10.0 statistical packages. Data are presented as means ± SD or means ± SE. Logarithmic transformation was used for insulin concentrations, HOMA-IR and $S_I$ index because of the high degree of skewing. Analysis for linear trend was carried out by ANOVA. A *P*-value less than 0.05 was considered statistically significant.

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## References

1. S.E. Kahn, J. Clin. Endocrinol. Metab. **86**, 4047–4058 (2001)
2. F. Vendrame, P.A. Gottlieb, Endocrinol. Metab. Clin. North Am. **33**, 75–92 (2004)
3. S. Genuth, K.G. Alberti, P. Bennett, J. Buse, R.A. Defronzo, R. Kahn, J. Kitzmiller, W.C. Knowler, H. Lebovitz, A. Lernmark, D. Nathan, J. Palmer, R. Rizza, C. Saudek, J. Shaw, M. Steffes, M. Stern, J. Tuomilehto, P. Zimmet, Diabetes Care **26**, 3160–3167 (2003)
4. M. Hanefeld, C. Koehler, K. Fuecker, E. Henkel, F. Schaper, T. Temelkova-Kurktschiev, Diabetes Care **26**, 868–874 (2003)
5. E. Ferrannini, A. Gastaldelli, Y. Miyazaki, M. Matsuda, M. Pettiti, A. Mari, R.A. DeFronzo, Diabetologia **46**, 1211–1219 (2003)
6. J. Hong, M.H. Gui, W.Q. Gu, Y.F. Zhang, M. Xu, Z.N. Chi, Y. Zhang, X.Y. Li, W.Q. Wang, G. Ning, Diabet. Med. **25**, 73–79 (2008)
7. M.A. Abdul-Ghani, C.P. Jenkinson, D.K. Richardson, D. Tripathy, R.A. DeFronzo, Diabetes **55**, 1430–1435 (2006)
8. N. Unwin, J. Shaw, P. Zimmet, K.G. Alberti, Diabet. Med. **19**, 708–723 (2002)
9. Y.F. Zhang, J. Hong, W.W. Zhan, X.Y. Li, W.Q. Gu, Y.S. Yang, M. Xu, G. Ning, Clin. Endocrinol. (Oxf) **64**, 153–157 (2006)
10. No author listed, Diabetes Care **20**, 1183–1197 (1997)
11. R.A. DeFronzo, J.D. Tobin, R. Andres, Am. J. Physiol. **6**, E214–E223 (1979)
12. C. Meyer, J. Hosker, A. Rudenski, B. Naylor, D. Treacher, R. Turner, Am. J. Physiol. **275**, F915–F921 (1998)
13. C. Weyer, C. Bogardus, D.M. Mott, R.E. Pratley, J. Clin. Invest. **104**, 787–794 (1999)
14. R.N. Bergman, M. Ader, K. Huecking, G.V. Citters, Diabetes **51**(suppl 1), S212–S220 (2002)
15. M. Kanazawa, N. Yoshiike, T. Osaka, Y. Numba, P. Zimmet, S. Inoue, Asia Pac. J. Clin. Nutr. **11**(Suppl), S732–S737 (2002)
16. J. Hong, W.Q. Gu, Y.F. Zhang, Y.S. Yang, C.F. Shen, M. Xu, X.Y. Li, W.Q. Wang, G. Ning, Endocrinology **31**, 93–99 (2007)
17. G.M. Steil, A. Volund, S.E. Kahn, R.N. Bergman, Diabetes **42**, 250–256 (1993)
18. S.E. Kahn, R.L. Prigeon, D.K. McCulloch, E.J. Boyko, R.N. Bergman, M.W. Schwartz, J.L. Neifing, W.K. Ward, J.C. Beard, J.P. Palmer, Diabetes **42**, 1663–1672 (1993)